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EXAMINER	
SCHNIZER, RICHARD A	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,726	KLIPPEL-GIESE ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-60* is/are pending in the application.

4a) Of the above claim(s) *41,42,46-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-40 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group 8 in the reply filed on 12/12/07 is acknowledged. Claims 41, 42, and 46-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 34-40 and 43-45 are under consideration to the extent that they read on methods of treating a disease or pathological condition associated with dysregulation of the PI-3 kinase pathway, comprising administering to a subject suffering from said disease an effective amount of an siRNA that inhibits the activity of PRF1.

Applicant's indication that the claims will be renumbered as required in the restriction requirement of 7/12/07 is acknowledged. Appropriate renumbering is required in response to this action.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.

(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Insertion of appropriate headings is suggested.

Drawings

The Drawings are objected to because Fig. 5 lacks labels for Panels A and B described in the brief description of the drawings.

Specification/Drawings/Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final

rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at Table 2, pages 43 and 44, and Fig. 6, panel b disclose nucleotide sequences in excess of 9 bases that are not accompanied by a SEQ ID NO.** If these sequences are listed in the current Sequence Listing, then the specification should be amended to include the appropriate SEQ ID NO in each of the passages referred to above. If these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951
- For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.
- Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov.

Claim Objections

Claim 38 is objected to because "diseases" in the third line should be singular, and "harmartoma" is misspelled in the fifth line.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is indefinite because it is unclear what are the metes and bounds of "unwanted" PRF1 activity.

Claim 44 is indefinite because it requires an siRNA molecule comprising a sequence of 50 nucleotides, but siRNAs are recognized in the art to be generally of 21-23 nucleotides in length. Elbashir et al (Genes Dev. Vol. 15, No. 2, pp. 188-200, January 15, 2001) originally identified siRNAs as 21-23 nucleotide dsRNAs that mediate RNA interference. Generally, siRNAs are considered to be dsRNAs that can participate in the formation of an RNA-induced silencing complex, e.g. products of dicer activity or synthesized dsRNAs that are 21-23 nucleotides in length. See also Kim et al (Nature Biotech. 23(2): 222-226, 2005) at abstract, and page 222, column 2, lines 1-4. RNA molecules of 50 nucleotides in length are not properly referred to as siRNAs.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 34-40 and 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of a tumor or a precancerous growth, wherein the tumor or precancerous growth is characterized by dysregulation of phosphoinositide 3-kinase (PI3K) signaling, by delivering directly to the tumor or precancerous growth an siRNA that causes degradation of an mRNA encoding PRF1, does not reasonably provide enablement for methods of inhibiting the growth of a tumor or a precancerous growth by systemic delivery of siRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 34, 39, 40, and 43-45 are directed to a method of treating any disease or pathological condition associated in any way with dysregulation of the phosphoinositide 3-kinase (PI3K) pathway by administering to a subject an effective amount of an siRNA that inhibits expression of PRF1.

Claim 35 requires that the dysregulation of the phosphoinositide-3 kinase pathway is associated with increased or unwanted activity of PRF1.

Claims 36-38 specify various cancers or precancerous disorders and diseases for treatment.

None of the claims limits the mode of administration.

Enabled Scope of Disease or Pathological Condition Treatment

PI3Ks constitute a family of enzymes that respond to stimuli from various receptors to produce 3' phosphoinositide lipids that act as second messengers by binding to diverse cellular target proteins to influence a variety of cellular activities including proliferation, differentiation, chemotaxis, survival/apoptosis, intracellular trafficking, and glucose homeostasis. See Katso et al (Annu. Rev. Dev. Biol. 17: 615-675, 2001). Katso states that the factors that determine which cellular function is mediated by a PI3K are complex and may be partly attributed to the diversity that exists at each level of the PI3K signaling cascade, such as the type of stimulus, duration of stimulus, the isoform of PI3K, the nature and intracellular location of the second messenger lipids, and the developmental state of the cell or organism. Further, the spatial and temporal aspects of PI3K signaling, functional redundancy, and crosstalk with other signaling networks are also thought to influence the integration of a given stimulus. See abstract, and page 655, first paragraph of Perspective.

Fig. 1 at page 624 of Katso gives some idea of the enormous complexity of PI3K signaling. Stimuli, both positive and negative, include Fak, shear stress, Cbl, Ruk, tyrosine kinase receptors, cytokines, integrins, cadherin, and G protein coupled receptors. Second messenger PIP_3 interacts with diverse entities including BTK/Tec kinases, PDKI, PKD, and GEFs. These interactions give rise to overlapping as well as independent cascades of activity that result in a variety of outcomes including proliferation, differentiation, chemotaxis, survival/apoptosis, trafficking, and glucose

homeostasis. Note that many factors known to be involved in PI3K signaling are not even represented in the Fig (such as Akt and HIF1-alpha). Thus, those of skill in the art at the time of the invention recognized that the effects of PI3K signaling in a given cell were influenced by a complex multitude of factors that constitute nodes in a network of signaling cascades extending from PI3K that controls the activity of a variety of proteins and the transcription of various sets of genes. The effects of manipulating any one of these nodes, such as PRF1, would be completely unpredictable in a given cell. Evidence of this comes from experiments in which a gene encoding the 85 kd PI3K regulatory subunit was knocked out. The predicted effect was to decrease glucose transport, but in fact an increase in glucose transport was observed. See Katso at page 644 and Table 2 at page 645.

Further evidence of unpredictability that is directly relevant to manipulation of PRF1 comes from Fig. 1 at page 624 which indicates that PI3K can have either positive or negative effects on apoptosis, depending on the status of the cell. The instant specification indicates that PRF1 is anti-apoptotic, so inhibition of PRF1 can stimulate apoptosis for therapeutic purposes. However, Fig. 1 discloses at least two other pathways by which PI3K can inhibit apoptosis (i.e. through stimulation of IKK or inhibition of BAD). Also Shoshani et al (Mol. Cell. Biol. 22(7): 2283-2293, 2002) taught that the function of RTP801 (PRF1) was dependent on the context of the cell in which it was expressed. PRF1 protected certain cells from apoptosis, but caused massive cell death in others, suggesting a complex type of involvement in pathogenesis. See abstract. Absent information regarding which pathways are operating in a given cell at

a given time, it would be completely unpredictable as to whether inhibition of PRF1 would stimulate apoptosis or not, because the effects of PRF1 inhibition on the other relevant apoptosis-affecting pathway is unknown. The specification provides no guidance in this regard. Note that the situation is further complicated by the fact that the status of PI3K independent signaling pathways would also need to be taken into account in order to accurately predict the effects of such inhibiting PRF1 (see Katso at page 656, last paragraph).

The instant invention is based on the observations that transcription of PRF1 is regulated by one or more of the diverse PI3K signaling pathways, and that inhibition of PRF1 expression in PC-3 prostate cancer cells resulted in a decrease in tumor growth. The specification presents evidence that this transcriptional activation occurs downstream of HIF1 alpha and Akt in two of the myriad PI3K pathways but provides no further guidance as to the biochemical function of PRF1 or its location in the PI3K signaling network. Generally speaking, the effect of a given node in the network should increase in specificity with the distance of that node from PI3K (see e.g. instant specification at page 17, first full paragraph). Accordingly, one of skill in the art would never reasonably expect to be able to treat the full scope of diseases or pathological disorders that can be associated with dysregulation of PI3K by manipulating any single node in the PI3K signaling network, because the effect of one node on any of the others is unpredictable. It is clear that not all aspects of the PI3K network are functional in all cells, so it follows that diseases that are caused by defects in separate PI3K pathways that are not functional in the same cell would not be treatable by an agent that affects

only one of the pathways. Furthermore, the pathway steps that lead directly to PRF1 transcription are unknown, as are the pathway steps directly downstream of PRF1 expression, and its possible interactions with other signaling pathways. Accordingly the effects of manipulating its expression are unpredictable and must be determined on a case by case basis for different cell types and different diseases.

The courts have addressed situations in which the operability of an invention is determined trial by error experimentation in an unpredictable setting. As set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

In this case the specification teaches a working example of the inhibition of growth of PC-3 tumor cells by inhibition of PRF1 expression, and the prior art teaches that dysregulation of PI3K can contribute to cellular transformation (e.g. by mutation of tumor suppressor PTEN, amplification of growth hormone receptors that stimulate PI3K, or mutation of stimulatory Ras, all of which can lead to unregulated PI3K activity and accumulation of phosphoinositides, see Katso at page 648, lines 2-7). However, this is not commensurate in scope with the entire range of pathological conditions embraced by the claims in view of the specification, including e.g. diabetes and wound healing (see abstract).

Accordingly one of skill would have to perform undue experimentation in order to treat the embraced scope of diseases and pathological conditions embraced by the claims.

Enabled Scope of Delivery Modes

Those of skill in the art at the time of the invention, and after the invention, recognized significant obstacles related to the predictability of inhibiting expression of a target gene *in vivo* by RNA interference (RNAi), particularly in regards to the *in vivo* targeting and delivery of specific nucleic acids that mediate RNAi to the appropriate cell/organ, at a bio-effective concentration and for a period of time such that said molecule is effective in inhibiting expression of a target gene. Indeed, nucleic acid based therapies at the time of filing were highly unpredictable and while it is recognized that introduction of dsRNA targeted to a specific gene may result in expression inhibition, the successful delivery of dsRNA to a target cell *in vivo*, such that the requisite biological effect was provided to the target cells/tissues/organs, must be determined empirically.

The state of the art at the time of filing shows that RNA interference was recognized as not enabled for therapeutic purposes. (See for example, Caplen 2003, Expert Opin. Biol. Ther. 2003, Vol. 3, pp. 575-586; Coburn et al. 2003, Journal of Antimicrobial Chemotherapy. Vol. 51, pp. 753-756; Agami et al. 2002 Current Opinion in Chemical Biology. Vol. 6, pp. 829-834) for reviews on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pp. 503-514) stated, "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA", and in column 2 of the same page, "[a]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (pg. 581).

Coburn et al. (2003) taught that the major impediment to using RNA interference as a therapeutic is that suppression of gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph).

Check (Nature, 2003, Vol., 425, pp. 10-12) reported "...scientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up." (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " ...'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page, "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

After the time of the invention, Zhang et al (Current Pharmaceutical Biotechnology 2004, Vol. 5, pp.1-7) reviewed the state of the art with regard to RNAi, and stated "[u]se of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Thus it is abundantly clear that it was not routine prior to and after the time of the invention for those of skill in the art to perform therapy by delivery of siRNA to target

cells in vivo, particularly by methods other than those that allow delivery directly to the target cells.

In particular regards to Applicant's *ex vivo* example, often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al (Agrawal et al. (Mol. Med. Today 6:72-81, 2000) stated "[t]he cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*in vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discussed these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies").

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed does not disclose any delivery formulations or techniques that were not available in the prior art, and so does not adequately address the state of the art at the time of the invention with regard to siRNA delivery to target cells in vivo.

Given the recognized unpredictability in the art of nucleic acid therapeutics, one of skill would still require specific guidance to practice the claimed methods *in vivo* in

any organism or any mammal, with the resultant specified biological effect. However, the specification does not provide either examples or the required guidance to allow one of skill in the art to reliably and predictably obtain success using the claimed methods *in vivo*. The specification does not overcome the art recognized obstacles to *in vivo* RNAi, particularly in terms of specific targeting and delivery of the dsRNA to a whole organism. As a result one of skill in the art would have to perform undue experimentation in order to practice the claimed invention.

Based on the instant disclosure, one of skill in the art would not know, *a priori,* if practicing of the instant method comprising introducing a siRNA of the invention, *in vivo,* to a whole organism, would result in the successful inhibition of the target gene in any particular cell, tissue or organ of said organism. Thus one of skill in the art could not practice the invention commensurate in scope with the clams.

Claim Rejections - 35 USC § 102

The following rejections are directed to the invention as broadly claimed in the linking claims, not to the elected invention. They are set forth as a courtesy to Applicant as further evidence that the linking claims are not allowable, ad that rejoinder of linked inventions is not appropriate at this time.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34-37 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Hu et al (Clinical Cancer Research (2000 Mar) Vol. 6, No. 3, pp. 880-6).

Hu taught a method of inhibiting growth of ovarian cancer cells in a mouse by administration of LY294002, which is an inhibitor of PI3K (see abstract). The instant specification teaches that PI3K stimulates transcription of PRF1. It follows that inhibitors of PI3K will inhibit expression of PRF1. Absent evidence to the contrary Hu anticipates the claims.

Claims 34-37, 39, and 45 are rejected under 35 U.S.C. 102(a) as being anticipated by Allen et al (Sem. Oncol. 29(3): Suppl. 11: 11-21, 6/2002).

Allen taught a method in which CI-1033, an inhibitor of PI3K, was used to treat breast cancer. The instant specification teaches that PI3K stimulates transcription of PRF1. It follows that inhibitors of PI3K will inhibit expression of PRF1. Absent evidence to the contrary Allen anticipates the claims.

Claims 34-37, 39, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldenberg (Clinical therapeutics, (1999 Feb) Vol. 21, No. 2, pp. 309-18) as evidenced by Yakes et al (Cancer Research, (2002 Jul 15) Vol. 62, No. 14, pp. 4132-41).

Goldenberg taught a method of treating breast cancer in humans by administration of Trastuzumab (Herceptin). Yakes provides evidence that Trastuzumab inhibits PI3K signaling and Akt activity. The instant specification teaches that PI3K

stimulates transcription of PRF1 through the action of Akt. It follows that inhibitors of PI3K or Akt will inhibit expression of PRF1. Absent evidence to the contrary Goldenberg anticipates the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.
Primary Examiner